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09/807,720	04/18/2001	Henry Daniell	1462- PCT-US-00	4039

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EXAMINER	
KUBELIK, ANNE R	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/807,720	Applicant(s) DANIELL, HENRY
	Examiner Anne Kubelik	Art Unit 1638

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-18 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1-18 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 6 .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. Claims 1-18 are pending.

2. The draftsman has approved the drawings as submitted.

3. This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825.

Sequence identifiers are missing from the primers on pg 12 and the descriptions of Figures 1 and 3.

Full compliance with the sequence rules is required in response to this Office action. A complete response to this Office action must include both compliance with the sequence rules and a response to the issues set forth below. Failure to fully comply with both of these requirements in the time period set for in this Office action will be held to be non-responsive.

4. This application does not contain an abstract of the disclosure as required by 37 CFR 1.72(b). An abstract on a separate sheet is required.

Claim Objections

5. Claims 16-17 are objected to under 37 CFR 1.75(c) as being in improper form because a multiple dependent claim may not depend from another multiple dependent claim. See MPEP § 608.01(n). For purposes of examination, claims 16-17 were treated as though they were dependent solely upon claim 1. Such treatment does not relieve Applicant of the responsibility to respond to this objection.

6. Claims 1-18 are objected to because of the following informalities:

Claims 2-6, 8-14 and 16-18 start with improper articles.

In claim 15, "introducting" in line 2 is misspelled.

In claim 15, there is an improper article before "integration" in line 2.

An article is missing before "cytotoxic" in claim 1, line 4; "transcription" in claim 1, line 4; "plastid" in claim 7, line 1; "transgenic" in claim 14, line 1; and "antibiotic" in claim 14, line 2.

Claim Rejections - 35 USC § 112

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 1-18 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are broadly drawn to a multitude of plastid transformation vectors that comprise a plastid promoter, a selectable marker sequence, a nucleic acid encoding any cytotoxic antimicrobial peptide, transcription termination sequences, and flanking DNA sequences, to a plastid transformation vector that works in different plant species, to plants transformed with such vectors, and to a method of stably transforming a plant using those vectors. The vectors also include those that function in any plant because their flanking sequence are homologous to sequences in the plastid genome that are conserved in the plastids from a multitude of different plants species.

The specification fails to describe any plastid transformation vectors that encode a cytotoxic antimicrobial peptide. The structural features that distinguish all such nucleic acids from other nucleic acids are not provided.

Hence, Applicant has not, in fact, described the plastid transformation vectors of the claims, and the specification fails to provide an adequate written description of the claimed invention.

Therefore, given the lack of written description in the specification with regard to the structural and physical characteristics of the claimed compositions, it is not clear that Applicant was in possession of the genus claimed at the time this application was filed.

See *Univ. of California v. Eli Lilly*, 119 F.3d 1559, 43 USPQ 2d 1398 (Fed. Cir. 1997):

> The name cDNA is not in itself a written description of that DNA; it conveys no distinguishing information concerning its identity. While the example provides a process for obtaining human insulin-encoding cDNA, there is no further information in the patent pertaining to that cDNA's relevant structural or physical characteristics; in other words, it thus does not describe human insulin cDNA .... Accordingly, the specification does not provide a written description of the invention ....

and at pg 1406:

> a generic statement such as "vertebrate insulin cDNA" or "mammalian insulin cDNA," without more, is not an adequate written description of the genus because it does not distinguish the genus from others, except by function. It does not specifically define any of the genes that fall within its definition. It does not define any structural features commonly possessed by members of the genus that distinguish them from others. One skilled in the art therefore cannot, as one can do with a fully described genus, visualize or recognize the identity of the members of the genus. A definition by function, as we have previously indicted, does not suffice to define the genus because it is only an indication of what the genes does, not what it is.

See *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ 2d 1016 at page 1021:

> A gene is a chemical compound, albeit a complex one, and ... conception of a chemical compound requires that the inventor be able to define it so as to distinguish it from other materials .... Conception does not occur unless one has a mental picture of the structure of the chemical or is able to define it by its method of preparation, its physical or chemical properties, or whatever characteristics sufficiently distinguish it. It is not sufficient to define it solely by it principal biological property, *e.g.*, encoding human erythropoietin, because an alleged conception having no more specificity than that is simply a wish to know the identity of any material with that biological property.

9. Claims 1-18 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter that was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claims are broadly drawn to plastid transformation vectors that comprise an expression cassette comprising a plastid promoter, a selectable marker sequence, a nucleic acid encoding any cytotoxic antimicrobial peptide, transcription termination sequences, and flanking DNA sequences, to a plastid transformation vector that works in different plant species, to plants transformed with such vectors, and to a method of stably transforming a plant using those vectors.

The instant specification, however, only provides guidance for transformation of tobacco with a vector that comprises the MSI-99 (a substituted magainin II) gene (pg 9 and 12) and for PCR amplification of a portion of the plastid genome (pg 9-10 and 12). The specification describes a method of assaying the effect of total protein from transgenic plants on the growth of *Pseudomonas syringae* and *P. aeruginsa* (pg 10 and 12-13). The specification also describes a method of applying *P. syringae* to transformed and untransformed tobacco plants (pg 10 and 13).

The instant specification fails to provide guidance for the sequence of any plastid transformation vector that comprises an expression cassette comprising a plastid promoter, a selectable marker sequence, a nucleic acid encoding any cytotoxic antimicrobial peptide, transcription termination sequences, and flanking DNA sequences (including that used in the plants of the instant application) or for a plastid transformation vector that works in different plant species, for plants transformed with such vectors, or for a method to stably transform a plant using those vectors. The specification also fails to teach any plastid transformation vector that is

"universal" and that has flanking sequences that are homologous to spacer sequences that are conserved in the plastid genomes of different plant species. The specification fails to teach the sequences of all nucleic acids encoding cytotoxic antimicrobial peptides. The specification also fails to teach selectable marker sequences that allow selection in the absence of an antibiotic.

The region of the tobacco plastid genome commonly used for targeting of transformation vectors is not present in the same configuration in the plastid genomes of other economically important plants; for example, rice (Kanno et al, 1993, Curr. Genet. 23:166-174) lacks the orf131/orf70B gene (see Figure 3). The specification fails to teach a region of the plastid genome that is homologous across all plant species.

The specification mentions that tobacco was transformed at a lower efficiency when flanking sequences derived from petunia were used than when flanking sequence derived from tobacco (pg 9 and 11). Figure 1 supposedly illustrates the petunia flanking sequence used, however, it consists only of a drawing and a peptide sequence and contains no DNA sequences. The instant specification fails to teach transformation of the plastids of any other plant species, including maize, rice, grass, rye, barley, oats, wheat, soybean, peanut, grape, sweet potato, pea, canola, tomato or cotton.

Expressing pesticidal peptides in plants is unpredictable. Okamoto et al (1998, Plant Cell Physiol. 39:57-63) transformed tobacco plants with a gene encoding a short antimicrobial peptide behind a constitutive promoter. The peptide was so unstable in plants that it could not be detected, even though the mRNA encoding it was expressed at high levels (pg 59, left column, last paragraph, to pg 60, entire left column). Similarly, Allefs et al (1995, Am. Potato J. 72:437-445)

teach that potato plants transformed with a gene encoding the antimicrobial peptide cecropin B degrade the encoded peptide and have no increase in resistance to infection (pg 441-443).

Even when peptides are not degraded in the transgenic plants, they unexpectedly do not retain their biological activity. Peptides that are effective pesticides when isolated and contacted with microorganisms or fed to insects do not function as pesticides when genes encoding them are transformed into plants. When tobacco plants were transformed with a gene encoding cecropin B, the transformed plants displayed no increase in disease resistance (Hightower et al, 1994, Plant Cell Rep. 13:295-299, see pg 297, paragraph spanning the columns, to pg 298, right column, paragraph 1). De Bolle et al (1996, Plant Mol. Biol. 31:993-1008) teach that tobacco plants transformed with genes encoding seed antimicrobial peptides had no increase in resistance to infection (pg 1004, paragraph spanning the columns).

As the specification does not describe the transformation of all plants with a vectors encoding cytotoxic antimicrobial peptides, undue trial and error experimentation would be required to screen through the myriad of nucleic acids encompassed by the claims and plants transformed therewith, to identify those with that are bacteria-resistant, if such plants are even obtainable.

10. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

11. Claims 1-18 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter that Applicant regards as the invention. Dependent claims are included in all rejections.

Claim 1 lacks antecedent basis for the limitations "said plastid" in line 3, "the target plastid genome" in line 6, "the heterologous coding sequence" in line 7, "the plastid genome" in line 7, "the target plant" in line 7, "the flanking sequence" in line 8 and "the homologous sequences" in lines 8-9.

It is unclear in claim 1 what is means for a vector to be stable and how a stable vector differs from an unstable one.

Claim 1 is indefinite in its recitation of "transcription termination functional" in lines 4-5. It is unclear what a transcription termination is and in what manner it would be functional. A word, possibly --sequence--, appears to be missing after "termination".

Claim 2 is not written in proper Markush format. Because "plastid" in line 1 is singular, to be grammatically consistent all members of the groups must be singular. See MPEP § 2173.05(h).

Claim 3 lacks antecedent basis for the limitation "the antimicrobial peptide" in line 1

Claim 3 is not written in proper Markush format. The claim should be in the format "selected from the group consisting of A, B, C and D." in line 2, "groups" should be replaced with -- group consisting--. Additionally, as "peptide" in line 1 is singular, all members of the groups should also be singular to be grammatically consistent. See MPEP § 2173.05(h).

Claim 3 is indefinite in its recitation of the abbreviation "PGLA", which is not defined in the specification.

In claim 4, "antimicrobial peptide" should be replaced with --magainin-- or the claim should be made dependent upon claim 1.

Claim 5 is indefinite in its recitation of "wherein the selectable marker sequence is an antibiotic-free selectable marker". Applicant appears to be equating a DNA sequence with what it encodes.

Claim 6 lacks antecedent basis for the limitation "A universal integration and expression vector of claim 1".

Claim 6 "vector ... competent for stably transforming a plastid genome". The phrase --wherein the vector is-- should be inserted before "competent". It is also unclear what it means for a vector to be competent for stably transforming something.

It is unclear in claim 6 what the phrase starting with "wherein" is intended to modify. It currently modifies "species". It is suggested that --and-- be inserted before "wherein".

It is unclear in claim 6 how many different plant species the vector is "competent" for transforming and the sequence is conserved within.

Claim 6 lacks antecedent basis for the limitations "the flanking DNA sequences" and "the sequence". Claims 1 and 6 refer to many different sequences, and it is not clear to which "the sequence" refers.

Claim 7 is indefinite in its recitation of "the progeny thereof". It is not clear if the progeny are of the vectors of claims 1-6, the plastid or the plant.

In claims 7 and 13, the word "including" renders the claims indefinite because it is unclear whether the limitations following the word are part of the claimed invention. See MPEP § 2173.05(d). If Applicant intends to claim the seeds as well as the plants, it is improper to claim more than one product in a single claim.

In claims 8-11, "which" should be replaced with --, wherein the plant--

In claim 10, an article should be inserted after "is" and --plant-- should be inserted after "cotton".

In claim 11, it is unclear what is meant that a plant is "edible for mammals and humans" as any plant can be eaten. Additionally, it is not clear why humans are mentioned separately, as they are mammals.

In claims 12-14, "in which" should be replaced with --, wherein --

Claim 12 lacks antecedent basis for the limitation "all the chloroplasts".

It is unclear in claim 12, what it means for chloroplasts to be uniformly transformed.

Claim 13 lacks antecedent basis for the limitations "the transformed plastid of the plants". Additionally, it appears that all the plants share a single plastid.

In claim 13, it is unclear which gene has enhanced levels of expression or if it even is a gene that has enhanced levels of expression. The claim is also indefinite in its recitation of "capable of" as it is not clear if enhanced levels of expression are required.

Claim 14 appears to be missing words and makes no sense.

In claim14, the word "like" renders the claim indefinite because it is unclear whether the limitations following the word are part of the claimed invention. See MPEP § 2173.05(d). Additionally, spectinomycin is not a marker sequence.

Claims 15 and 18 are indefinite because they lack agreement between the preamble of the methods and the positive method steps. Methods must be circular; the final step must generate the item the method is intended to produce. For example, the method of stably transforming a plant to control phytopathogenic bacteria in claim 15 ends in allowing a plant to grow, when it should end in the control of phytopathogenic bacteria.

In claim15, "which" should be replaced with --, wherein the method--. As it stands, the phrase starting with "which" modifies "bacteria".

Claim 15 lacks antecedent basis for the limitations "an integration and expression vector of claims 1, 2, 3, 4, 5 or 6" in lines 2-3 and "the transformed plant" in line 3.

Claims 16-17 are indefinite for being improper multiple dependent claims.

Claim 16 lacks antecedent basis for the limitations "the target bacteria" in line 3 and "the target microbe" in line 4 and "the bacteria" in line 5.

The "functional to form aggregates" and the "functional ... in the prevention" language in lines 3-5 of claim 16 is awkward and ungrammatical.

It is not clear in claims 17 and 18 where the rbs and the 5' UTR are located relative to the other components of the vector.

Claim Rejections - 35 USC § 103

12. The following is a quotation of 35 U.S.C. 103(a), which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

13. Claims 1-18 rejected under 35 U.S.C. 103(a) as being unpatentable over Maliga et al (US Patent 5,877,402, filed January, 1994) in view of Davies et al (WO 90/11770).

The claims are drawn to plastid transformation vectors that comprise a plastid promoter, a selectable marker sequence, a nucleic acid encoding any cytotoxic antimicrobial peptide, transcription termination sequences, and flanking DNA sequences, to a plastid transformation

vector that works in different plant species, to plants transformed with such vectors, and to a method of stably transforming a plant using those vectors. The antimicrobial peptides include defensin and magainin.

Maliga et al disclose plastid transformation vectors comprising the plastid *psbA*, *rps16* or *Prrn* promoters operably linked to the *aadA* gene, the 3' region of the plastid *psbA* or *rps16* genes, a multicloning site, and flanking DNA sequences for targeting to the plastid genome (the *rbcL* sequence and the ORF512 sequence) (Figures 19C-G and 20C-F; column 56, line 1-56). Maliga et al also disclose plastid transformation vectors that comprise the *Prrn* promoter operably linked a kanamycin resistance gene, the 3' region of the plastid *psbA* gene, and flanking DNA sequences (Figures 8 and 9E; column 38, line 25, to column 43, line 47). Maliga et al disclose such plastid transformation vectors in which the *aadA* gene and the *uidA* gene are transcribed from the same promoter (Figures 22A-C; column 61, line 55, to column 63, line 16; column 63, lines 49-67). The vectors of Maliga et al also have a 5' UTR (Figure 22A-C) and a ribosome binding site (claims 16 and 24). Maliga et al do not disclose plastid transformation vectors encoding a cytotoxic antimicrobial peptide.

Davies et al teach that amtimicrobial peptides like defensins and magainins can be used to limit the growth of bacterial and fungal plant pathogens (pg 4, lines 21-28). Davies et al also teach plants transformation vectors encoding defensin or magainin (pg 24-47) and Brassica plants transformed with the vectors (pg 47-50).

At the time the invention was made, it would have been obvious to one of ordinary skill in the art to modify the method of plastid transformation taught by Maliga et al, to transform plant plastids with a vector encoding an antimicrobial peptide described by Davies et al. One of

ordinary skill in the art would have been motivated to do so because Maliga et al suggest using the vectors to transform plant plastids with genes conferring resistance to plant pathogens (column 27, lines 34-42).

14. Claims 1-18 are rejected under 35 U.S.C. 103(a) as being unpatentable over Maliga et al (US Patent 5,877,402, filed January, 1994) in view of Smith et al (WO 99/06564).

The claims are drawn to plastid transformation vectors that comprise a plastid promoter, a selectable marker sequence, a nucleic acid encoding any cytotoxic antimicrobial peptide, transcription termination sequences, and flanking DNA sequences, to a plastid transformation vector that works in different plant species, to plants transformed with such vectors, and to a method of stably transforming a plant using those vectors. The antimicrobial peptides include PGLA and magainin.

The teachings of Maliga et al are described above. Maliga et al do not disclose plastid transformation vectors encoding a cytotoxic antimicrobial peptide.

Smith et al teach that plants transformed with nucleic acids encoding magainin or PGL are resistant to fungi (pg 3, lines 26-31, and pg 10-12). Smith et al teach nucleic acids encoding substitution derivatives of magainin and PGL (pg 6, lines 20-26, and pg 12-15) and a derivative of cecropin A (pg 6, line 27-29 and pg 12-15). Smith et al also teach petunia, geranium, poinsettia, and lisianthus plants transformed with the nucleic acids (pg 15-18) and that the plants are resistant to fungi and bacteria (pg 18-34).

At the time the invention was made, it would have been obvious to one of ordinary skill in the art to modify the method of plastid transformation taught by Maliga et al, to transform plant plastids with a vector encoding an antimicrobial peptide described by Smith et al. One of

ordinary skill in the art would have been motivated to do so because Maliga et al suggest using the vectors to transform plant plastids with genes conferring resistance to plant pathogens (column 27, lines 34-42). Additionally, Smith et al suggest expression of these nucleic acids in plant plastids (pg 5, lines 3-11, and pg 9, lines 23-27).

Conclusion

15. No claim is allowed.

16. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anne R. Kubelik, whose telephone number is (703) 308-5059. The examiner can normally be reached Monday through Friday, 8:30 am - 5:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Amy Nelson, can be reached at (703) 306-3218. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 872-9306 for regular communications and (703) 872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the patent analyst, Kimberly Davis, at (703) 305-3015.

Anne R. Kubelik, Ph.D.
June 25, 2002

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